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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,649	DAHM ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *77-85* is/are allowed.

6)☒ Claim(s) *36-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-35 have been canceled. Claims 36-87 have been added. Claims 36-87 are pending and examined on the merits.

Claim Objections

Claim 41 is objected to because of the following informalities: use of the trade names "Percoll" and "Ficoll" without indication of the Trademark. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57, 86 and 87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 recites "wherein said method further comprises forming an interphase enriched in the non-tumor cells having telomerase activity and the telomerase positive cells and depleted from telomerase positive non-tumor cells". It appears part of the active method step is missing. It is unclear what is depleted from telomerase positive non-tumor cells.

Claim 86 recites "the flap opens into the lower compartment can opens from the outer edge" which is non-sensical. For purpose of examination, the phrase will be read as "the flap opens into the lower compartment from the outer edge".

Claim 87 is rendered vague and indefinite due to dependency on a canceled claim. For purpose of examination claim 87 will be read as dependent upon claim 36.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for

patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 36-47, 57-63 and 87 are rejected under 35 U.S.C. 102(e) as being anticipated by Ts'o et al (US 5,962,237) as evidenced by Wang et al (US 2002/0098535, priority to provisional applications 60/159,558 and 60/119,460) and the abstract of Soria (Clinical Cancer Research, 1999 May, Vol. 5, pp. 971-975).

Claim 36 is drawn to a method for separating tumor cells from a body fluid, comprising centrifuging in a centrifuge vessel a cell separation medium overlaid with a body fluid, wherein the cell separation fluid medium has a density in the range from 1.055 to 1.065 g/ml. Claim 37 embodies the method of claim 36 wherein the cell separation medium has a density in the range from 1.059 to 1.062 g/ml. Claim 38 embodies the method of claim 36 wherein the cell separation medium has a density of about 1.060 g/ml. Claim 39 embodies the method of claim 36 wherein centrifuging is carried out at about 500 to 2000 G for about 10 to 30 minutes. Claim 40 embodies the method of claim 36 wherein centrifugation is carried out at about 1000 G for about 20 to 30 minutes. Claim 41 embodies the method of claim 36 wherein the cell separation medium is selected from the group consisting of Percoll and Ficoll. Claim 42 embodies the method of claim 36 wherein said body fluid comprises one or more substances which prevent aggregation of platelets onto tumor cells. Claim 43 embodies the method of claim 36 wherein the body fluid has been treated to remove substances which promote aggregation of platelets onto cells. Claim 44 embodies the method of claim 36 wherein the body fluid is peripheral blood. Claim 45 embodies the method of claim 36 wherein the body fluid is peripheral blood mixed with an anticoagulant and diluted with a diluting medium. Claim 46 embodies the method of claim 36 wherein the peripheral blood is venous or arterial blood. Claim 47 embodies the method of claim 36 wherein the body fluid is selected from the group consisting of lymph, urine, exudates, transudates, spinal fluid, seminal fluid, saliva, fluids from natural or unnatural body cavities, bone marrow and dispersed body tissue.

Claim 57 embodies the method of claim 36 wherein the body fluid comprises non-tumor cells having telomerase activity and telomerase positive tumor cells, and wherein said method

further comprises forming an interphase enriched in the non-tumor cells having telomerase activity and the telomerase-positive cells and depleted from telomerase positive no tumor cells. Claim 58 embodies the method of claim 36 wherein the body fluid comprises tumor cells and blood stem cells, and said method further comprises a first step wherein an interphase is formed enriched in the tumor cells and the blood stem cells and a second step wherein the blood stem cells or the tumour cells are either enriched or depleted. Claim 59 embodies the method of claim 58 wherein the cell separation fluid medium has a density in the range from 1.055 to 1.065 g/ml. Claim 60 embodies the method of claim 58 wherein the cell separation medium has a density in the range from 1.059 to 1.062 g/ml. Claim 61 embodies the method of claim 58 further comprising separating the tumor cells from the blood stem cells. Claim 62 embodies the method of claim 58 further comprising separating the tumor cells from the blood stem cells by immunoadsorption. Claim 63 embodies the method of claim 58 wherein said body fluid is selected from the group consisting of bone marrow and peripheral blood.

Claim 87 is drawn to a tumor cell cultured obtained by a method as claimed in claim 36 [1].

Ts'o et al disclose a method for separating tumor cells form a body fluid comprising centrifuging said body fluid in a cell separation medium having a density in the range from about 1.06 g/ml to about 1.10 gm/ml (column 9, line 66 to column 10, line 3) . Ts'o et al disclose that for the enrichment of cancer cells from blood, a first density gradient medium having a density of 1.067 g/ml is preferred (column 9, line 62 to column 10, line 4). Ts'o et al teach the use if PercollTM or Ficoll for the cell separation (column 8, line 50 to column 9, line 24). Ts'o et al disclose that peripheral blood can be diluted with a diluting agent prior to placing it on a density gradient column (column 9, lines 25-44). Ts'o et al do not specifically disclose that the peripheral blood was treated with an anti-coagulant prior to loading on the density gradient column, however Ts'o et al states that "Twenty ml of fresh blood was taken in two tubes". It is standard in the art to have anti-coagulant substance such as heparin in blood collection tubes. Further, it is noted that Ts'o et al disclose plasma as a diluent for peripheral blood rather than serum (column 7, lines 43-45), further substantiating the use of peripheral blood wherein clotting has been prevented by the addition of an anti-coagulant. Ts'o et al disclose examples of bodily fluids as blood, urine, saliva, , lymph, spinal fluid, semen, amniotic fluid, cavity fluids and tissue

extract (column 5, lines 48-51). Ts'o et al disclose that the rare cells are cancer cells from localized and non-localized cancer such as carcinomas of the brain, breast, bladder, colon, kidney, liver, lung, ovary, pancreas, prostate, rectum and stomach in addition to sarcomas, cancerous hematopoietic cells, melanoma, teratocarcinoma, neuroblastoma and glioma. Ts'o et al teach that centrifugation is carried out from 300XG to 600XG or higher for 1-60 minutes (column 9, lines 44-61). Tso' et al teach a method of forming an interface enriched in "lighter" tumor cells and an interface enriched in "heavier" tumor cells, and the use of negative selection methods to remove non-tumor cells from the tumor cells comprising immunoadsorption (column 6, line 35 to column 8, line 33 and column 10, lines 45-55). Ts'o et al do not specifically teach that the bodily fluid comprises non-tumor cells having telomerase activity and telomerase positive tumor cells, however, it would be inherent in the interface of rare cells isolated by the method of Ts'o et al that the cancer cells would be telomerase positive as evidenced by the abstract of Soria et al which teaches that circulating epithelial cells in metastatic breast cancer are telomerase positive. Further Wang et al (US 2002/0098535) teach that some of the tumor cells recovered from the density gradient separation of Ts'o et al contain "stem-cell like cancer cells" which appears as an undifferentiated stem cell [0055], thus it would be inherent in the method of Ts'o et al that non-tumor stem cells would be present in the interface with stem-cell-like tumor cells. The non-tumor stem cells would inherently be telomerase positive.

Ts'o et al teach that rare cells isolated by the disclosed methods can be cultured in vitro, thus fulfilling the specific embodiments of claim 87 (column 16, lines 7-12).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36-53, 55, 57-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over. Ts'o et al anticipate the embodiments of claims 36-47, 57-63 for the reasons set forth above.

Claim 48 embodies the method of claim 36 wherein the lower portion of the centrifugation vessel is cooled before removing the interface enriched in tumor cells. Claim 49 embodies the method of claim 36 wherein the centrifugation vessel is divided into an upper compartment and a lower compartment. Claim 50 embodies the method of claim 49 wherein the upper and lower compartments are separate by a porous barrier, filter, or sieve. Claim 51 embodies the method of claim 50 wherein the porous barrier, or sieve has a thickness of 0.5-10 mm. Claim 52 embodies the method of claim 50 wherein the porous barrier or sieve has a thickness of 1-5 mm. Claim 53 embodies the method of claim 50 wherein the porous barrier or sieve has a pore size of 20-100 mm. Claim 55 embodies the method of claim 50 wherein the porous barrier or sieve comprises or is coated with a hydrophobic material.

Claim 64 is drawn to a kit for the separation of tumor cells from a body fluid comprising a cell separation medium which has a density in the range from 1.055 to 1.065 g/ml. Claim 65 embodies the kit of claim 64 further comprising a centrifugation vessel. Claims 66 and 68 embody the kit of claim 64 wherein the cell separation medium has a density in the range of 1.059- 1.061 g/ml and 1.061 g/ml to 1.065 g/ml, respectively. Claims 67 and 69 embody the kit of claim 64 wherein the cell separation medium has a density of about 1.060 g/ml and 1.062 g/ml, respectively.

Claim 70 embodies the kit of claim 64 wherein the centrifugation vessel is divided into an upper compartment and a lower compartment. Claim 71 embodies then kit of claim 70 wherein the upper and lower compartments are separate by a porous barrier, filter, or sieve. Claim 72 embodies the kit of claim 71 wherein the porous barrier, or sieve has a thickness of

about 0.5 to 10 mm. Claim 73 embodies the kit of claim 71 wherein the porous barrier, or sieve has a thickness of about 1-5 mm. Claim 74 embodies the kit of claim 71 wherein the porous barrier or sieve has a pore size of 20-100 mm. Claim 76 embodies the kit of claim 64 comprising a centrifugation vessel wherein the separation medium is present in the lower compartment.

Ts'o et al disclose a method for separating tumor cells form a body fluid comprising centrifuging said body fluid in a cell separation medium having a density in the range from about 1.06 g/ml to about 1.10 gm/ml (column 9, line 66 to column 10, line 3) . Ts'o et al disclose that for the enrichment of cancer cells from blood, a first density gradient medium having a density of 1.067 g/ml is preferred (column 9, line 62 to column 10, line 4). Ts'o et al teach the use if PercollTM or Ficoll for the cell separation (column 8, line 50 to column 9, line 24). Ts'o et al disclose that peripheral blood can be diluted with a diluting agent prior to placing it on a density gradient column (column 9, lines 25-44). Ts'o et al do not specifically disclose that the peripheral blood was treated with an anti-coagulant prior to loading on the density gradient column, however Ts'o et al states that "Twenty ml of fresh blood was taken in two tubes". It is standard in the art to have anti-coagulant substance such as heparin in blood collection tubes. Further, it is noted that Ts'o et al disclose plasma as a diluent for peripheral blood rather than serum (column 7, lines 43-45), further substantiating the use of peripheral blood wherein clotting has been prevented by the addition of an anti-coagulant. Ts'o et al disclose examples of bodily fluids as blood, urine, saliva, , lymph, spinal fluid, semen, amniotic fluid, cavity fluids and tissue extract (column 5, lines 48-51). Ts'o et al disclose that the rare cells are cancer cells from localized and non-localized cancer such as carcinomas of the brain, breast, bladder, colon, kidney, liver, lung, ovary, pancreas, prostate, rectum and stomach in addition to sarcomas, cancerous hematopoietic cells, melanoma, teratocarcinoma, neuroblastoma and glioma. Ts'o et al teach that centrifugation is carried out from 300XG to 600XG or higher for 1-60 minutes (column 9, lines 44-61). Tso' et al teach a method of forming an interface enriched in "lighter" tumor cells and an interface enriched in "heavier" tumor cells, and the use of negative selection methods to remove non-tumor cells from the tumor cells comprising immunoadsorption (column 6, line 35 to column 8, line 33 and column 10, lines 45-55). Ts'o et al do not specifically teach that the bodily fluid comprises non-tumor cells having telomerase activity and telomerase positive tumor cells, however, it would be inherent in the interface of rare cells isolated by the

method of Ts'o et al that the cancer cells would be telomerase positive as evidenced by the abstract of Soria et al (Clinical Cancer Research, 1999 May, Vol. 5, pp. 971-975) which teaches that circulating epithelial cells in metastatic breast cancer are telomerase positive. Further Wang et al (US 2002/0098535) teach that some of the tumor cells recovered from the density gradient separation of Ts'o et al contain "stem-cell like cancer cells" which appears as an undifferentiated stem cell [0055], thus it would be inherent in the method of Ts'o et al that non-tumor stem cells would be present in the interface with stem-cell-like tumor cells. The non-tumor stem cells would inherently be telomerase positive.

Ts'o et al teach a kit for the enrichment of cancer cells from blood comprising a density gradient medium of at least about 1.067 (column 12, lines 31-48). Ts'o et al do not teach a kit comprising a density gradient medium of less than 1.067. However, Ts'o et al teach that the density gradient medium may range from 1.06 to 1.10 g/ml (column 9, line 66 to column 10, line 3). Ts'o do not specifically teach that the centrifugation vessel is cooled prior to removal of the interface comprising the tumor cells

It would have been prima facie obvious at the time the invention was made to make a kit having density gradient medium ranging from 1.06 to 1.10). One of skill in the art would have been motivated to do so by the teachings of Ts'o et al on the range of density gradients appropriate for the separation of cancer cells from peripheral blood. One of skill in the art would be motivated to screen a number of densities in the range reported by Ts'o et al in order to optimize the separation. Thus, having a number of density gradients available in a kit would save time for the initial optimization. Further, it would have been obvious to provide a centrifugation vessel comprising a porous piece of plastic or sieve in order that the bodily fluid can be quickly loaded into the centrifugation vessel and retained before subjecting to centrifugation. One of skill in the art would have been motivated to make such an alteration in the centrifugation vessel in order to process multiple samples: having a porous plastic barrier would prohibit the mixing of the sample of bodily fluid with the cell separation medium until the tubes were subjected to centrifugal force. Thus, multiple samples could be "loaded" with the sample of bodily fluid and placed in the centrifuge at one time without allowance for variability in mixing with the cell separation medium that would occur as an experimental variable without the porous barrier separating the upper compartment and the lower compartment. Further, the

presence of a plastic support for a porous barrier, or a plastic porous barrier or the same substance as the centrifugation vessel would fulfill the specific embodiment of claim 55 drawn to a hydrophobic material. The dimensions of the plastic support for a porous barrier or a plastic porous barrier would obviously be similar to the thickness of the centrifugation vessel itself and thus render obvious claims 52 and 55 drawn to specific thickness.

It would also have been prima facie obvious to cool the density gradient prior to the removal of the interface comprising the tumor cells. One of skill in the art would know that this is standard procedure in the biological arts in order to slow down or halt enzymic reactions within the cells in the interface which could lead to the death and apoptosis of said cells. One of skill in the art would be motivated to isolate intact circulating cancer cells for diagnostic purposes. The death of the cancer cells during the gradient separation would not lead to a representative sample of circulating cancer cells.

Claims 36-55 and 57-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 36-53, 55, 57-74 above, and further in view of Wang et al (U.S. 2002/0098535, priority to 60/119,460).

Ts'o et al render obvious the specific embodiments of claims 36-53, 55, 57-74 for the reasons set forth above.

Claim 54 is drawn to the method of claim 50 wherein the porous barrier the filter or sieve has pore size of 20-30 mm. Claim 75 is drawn to the kit of claim 71 wherein the porous barrier the filter or the sieve has a pore size of 20-30 mm.

Ts'o et al as evidenced by Wang et al do not teach or render obvious a porous barrier, filter, or sieve having a pore size of 20-30 mm.

Wang et al teach circulating cancer cells which are "stem-cell like" cancer cells having a diameter of about 12-20 mm [0055-0057] in contrast to circulating cancer cells which are dying cancer cells having a diameter of about 30-50 mm .

It would have been prima facie obvious at the time the invention was made to use a porous barrier, filter, or sieve having a pore size of 20-30 mm in order to eliminate the terminal cancer cells from the tumor cell interface. One of skill in the art would have been motivated to do this by the teachings of Wang et al on the sizes of circulating terminal cancer cells versus

circulating stem-cell like cancer cells. One of skill in the art would known that the non-terminal stem-cell like cancer cells represents potential metastasis of a primary cancer, whereas circulating terminal cancer cells would not result in viable metastatic foci within a patient.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 36-47, 57-63 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'O et al (US 5,962,237) as evidenced by Wang et al and the abstract of Soria et al in view of the Pharmacia Biotech Catalog, 1997, page 5. The specific embodiments of claims 36-47, 57-63 and 87 and the teachings of Ts'o et al and Wang et al and the abstract of Soria et al which anticipate said claims are set forth above.

Claim 56 embodiments the method of claim 36 wherein the sell separation medium comprises a dye wherein said dye allows the cell separation medium to distinguish form the overlying body fluid by color and allows localization of an interphase enriched in tumor cells.

Neither Ts'o et al, Wang et al nor the abstract of Soria et al teach the use of dye to allow for the localization of an interphase enriched in tumor cells.

The Pharamacia Biotech Catalog teaches the use of color density marker beads within cell separation medium such as Percoll to allow for the determination of densities of cells separated on cell separation medium.

It would have been prima facie obvious at the time the invention was made to incorporate use of the colored density marker beads as taught by the Pharmacia Catalog. One of skill in the art would have been motivated to do so by the teachings of the Pharmacia Catalog on the ease of identifying a particular density by means of the colored beads included in the cell separation medium.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
6/28/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER